

## Case report

## Cowden's disease: A case report and review of the literature

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### SUMMARY

Cowden's syndrome, or multiple hamartoma syndrome, is a rare inherited disease with characteristic mucocutaneous lesions associated with multiple polyps of the gastrointestinal tract and abnormalities of the breast and thyroid gland. Cowden's disease carries a high risk of development of malignancies, especially of breast and thyroid. Rarely malformations and abnormalities occur in the skeletal system, central nervous system and urogenital tract.

Cowden's disease is included in the gastrointestinal (GI) polyposis syndromes. Multiple, usually non-adenomatous polyps throughout the GI tract, associated with skin and oral papules and oesophageal glycogenic acanthosis are considered pathognomonic signs for diagnosis.

We present a case of a 48 yr-old Greek female with Cowden's disease. The patient had facial papules, multiple GI hyperplastic polyps, oesophageal glycogenic acanthosis, goiter and had developed breast cancer two years previous to diagnosis. Gastroenterologists have to be aware of and recognize this unusual clinical entity because of its correlation with malignant tumors of the breast and thyroid.

**Key words:** Cowden's disease, Hamartoma, Hyperplastic polyp, PTEN gene, Gastrointestinal polyposis syndromes

### INTRODUCTION

Cowden's disease was first described in 1963 by Lloyd and Denis<sup>1</sup>. Since then approximately 150 additional cases have been reported in the literature. It is a rare autosomal, dominant, inherited disease characterized by multiple hamartomas and neoplasms of ectodermal, endodermal and mesodermal origin affecting many organs and systems. Mucocutaneous lesions have been reported in the literature with a high frequency (99-100%) and are the most characteristic features of the disease. They include multiple facial papules (trichilemmomas), acral keratoses and oral papillomatosis<sup>2,3</sup>. Multiple hamartomas and neoplasms of other organs, including thyroid tumors (benign and malignant), fibrocystic disease of the breast, breast carcinoma, neoplasms of the female genital tract and gastrointestinal polyps have also been reported<sup>3,4</sup>.

Gastrointestinal lesions are frequent (70-85%) in patients with Cowden's disease, though underestimated in earlier studies due to inadequate evaluation of the alimentary tract. Microscopically, the most common findings are hyperplastic polyps, hamartomas and ganglioneuromas of the stomach and bowel, especially sigmoid and rectum<sup>5,6</sup>. Recent genetic studies have shown association with a germ line mutation of the PTEN gene (10q 22-23). The PTEN is a tumor suppressor gene and its inactivation increases the risk of breast and thyroid cancer<sup>7</sup>.

In this report we present a case of a 48 year-old Greek female with Cowden's disease. We emphasize the endoscopic and histopathologic lesions of the GI tract, present a review of the literature and alert the gastroenterologists to consider the disease in the differential diagnosis of the gastrointestinal polyposis syndromes.

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## CASE REPORT

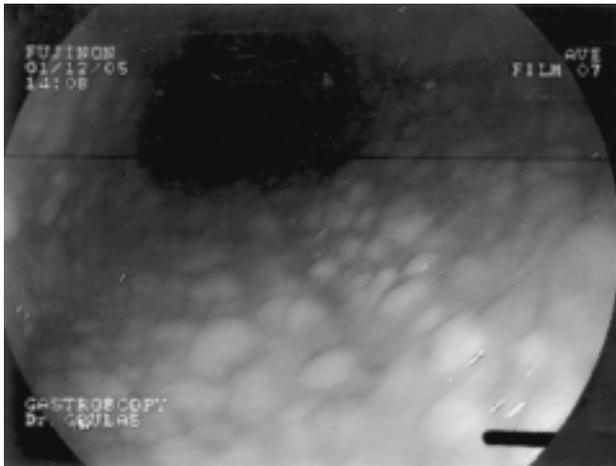
A 48-year-old female was admitted to the hospital for a laparoscopic cholecystectomy for cholelithiasis. Her symptoms were not typical of a biliary colic (epigastric discomfort, bloating) and she was referred to the GI unit for clinical evaluation. There was a long history of fibrocystic disease of the breast and of a right mastectomy, 2 years earlier, for an invasive breast carcinoma.

One of her sisters has a history of breast cancer and her daughter has von Recklinghausen's disease.

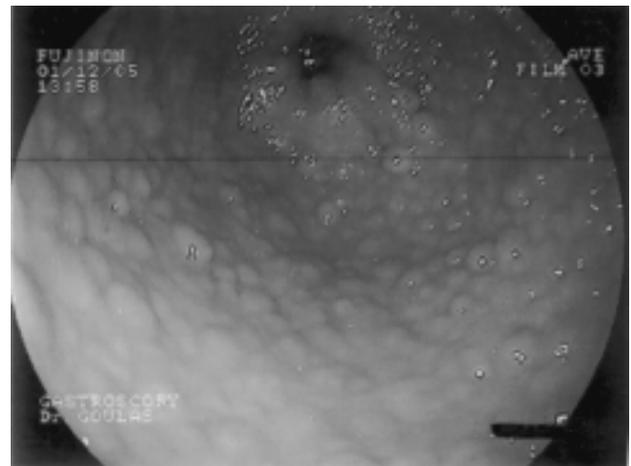
The physical examination was notable for isolated multiple soft facial papules around the lips and eyelids. The oral mucosa was normal. Her thyroid gland was enlarged and a recent ultrasound had revealed multiple

goiter. The thyroid function was normal and autoantibodies were negative.

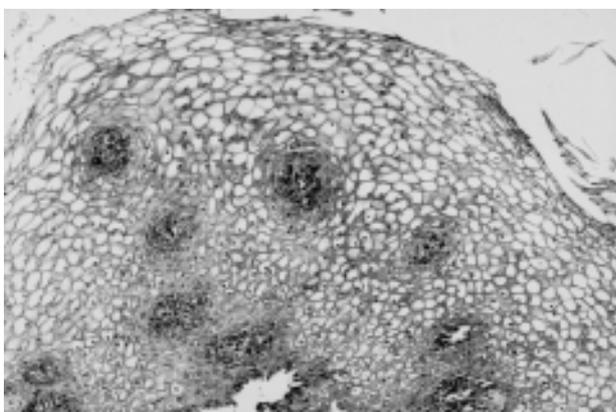
We performed an upper GI endoscopy which revealed extensive nodularity of the oesophagus, a micropolypoid appearance of the stomach (body and antrum) and a duodenal ulcer. The second part of the duodenum was normal. Biopsies were taken from the oesophagus and stomach. Histologic examination showed glycogenic acanthosis of the oesophagus with mild oesophagitis and mild chronic active gastritis without atrophy and a large load (grade 3) of *Helicobacter pylori* (Figures 1, 2). In view of the micropolypoid appearance of the gastric mucosa we went on to colonoscopy which revealed over 20 small polyps in the sigmoid and rectum, ranging in size from 0,2 to 0,4cm in diameter. The



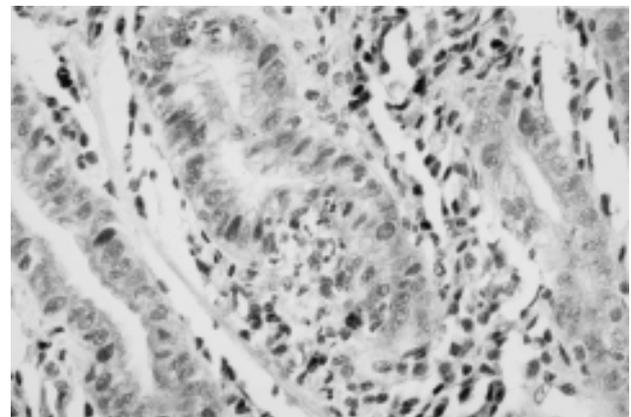
**Figure 1-a.** endoscopic image of multiple whitish nodules throughout the oesophagus.



**Figure 2-a.** endoscopic appearance of the micropolypoid gastric mucosa.



**Figure 1-b.** oesophageal mucosa showing mild inflammation and glycogenic acanthosis (H&E, x 100).

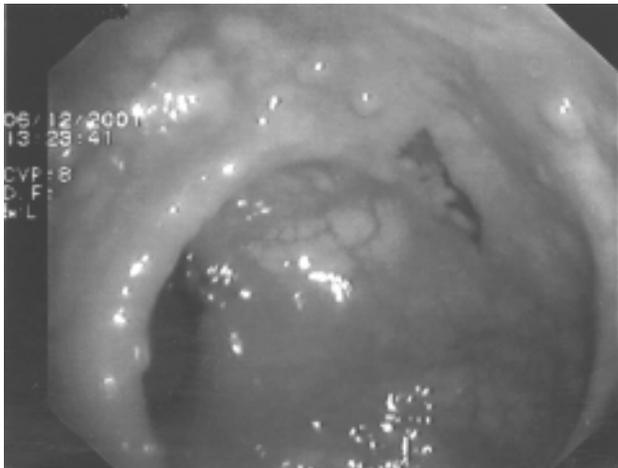


**Figure 2-b.** histologic appearance of superficial gastric mucosa with mild active inflammation (H&E, x 100).

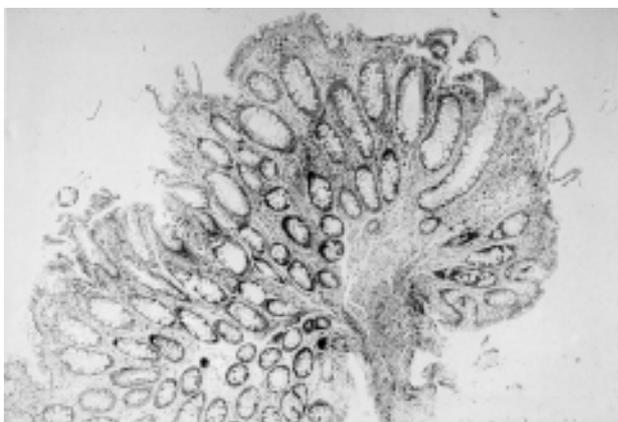
rest of the colon was normal. Biopsies were taken from seven sigmoid and three rectal polyps. Histologically all biopsies showed features of hyperplastic-type colonic polyp. Crypts showed mildly disturbed orientation and mild focal mucous depletion. Serrated borders were focally present but they were not a prominent feature of the polyps. The lamina propria was oedematous with mildly to moderately dense inflammatory infiltration by lymphocytes, plasma cells and focally foamy histiocytes. Occasional lymphoid follicles were also present (Figures 3a and 3b).

## DISCUSSION

Cowden's syndrome, or multiple hamartoma syn-



**Figure 3-a.** endoscopic appearance of the sigmoid colon with multiple polyps.



**Figure 3-b.** histologic appearance of a hyperplastic type sigmoid polyp (H&E, x 100).

drome, is an unusual autosomal, dominant, inherited disease with characteristic mucocutaneous lesions combined with gastrointestinal polyps and abnormalities in other organs with high frequency of malignant transformation, especially in the breast and thyroid, but notably not in the GI tract<sup>3,4</sup>. The disease is associated with a germ line mutation of the PTEN gene (10q 22-23)<sup>7</sup>. This rare clinical entity is well known to dermatologists and stomatologists because mucocutaneous lesions are the most obvious and characteristic features of the disease<sup>2-4</sup>.

GI lesions in Cowden's disease include multiple polyps, usually non-adenomatous, in the stomach, small and large bowel. The disease belongs to the spectrum of polyposis syndromes together with Familial Adenomatous Polyposis (FAP), Hereditary Non Polyposis Colon Cancer (HNPCC), Juvenile Polyposis and Peutz Jeghers syndrome<sup>7,8</sup>. In Cowden's syndrome the polyps are sessile or pedunculated and number from several to hundreds. The most frequent site of involvement is the sigmoid colon and rectum. Most polyps are hyperplastic, lipomatous, ganglioneuromatous, lymphoid and only occasionally adenomatous. These polyps have a very low - if any - malignant potential. The involvement of the oesophagus is common in the form of multiple whitish nodules, which histologically correspond to glycogenic acanthosis<sup>3,5,9,10</sup>.

The combination of oesophageal glycogenic acanthosis with multiple non adenomatous GI polyps and mucocutaneous papules is considered pathognomonic for the diagnosis of Cowden's syndrome<sup>5,11,12</sup>.

Our case is, to the best of our knowledge, the first documented case of Cowden's disease in Greece. The patient was unaware of her disease as the skin lesions were diagnosed as verrucae, the breast cancer and thyroid disease were considered and treated independently and there was no suspicion of this unusual clinical entity. She had multiple colonic hyperplastic polyps and oesophageal glycogenic acanthosis, which is a pathognomonic feature, according to the literature. The patient had already developed right breast cancer and thyroid goiter. Further evaluation of the thyroid gland and a careful examination and follow up of the left breast has been advised. Some authors recommend a prophylactic mastectomy to prevent a second malignancy<sup>12</sup>. Clinical evaluation of all first degree relatives is suggested as this is an autosomal dominant inherited disease.

Conclusively, the gastroenterologists have to be aware and consider this rare disease in the differential diagnosis of the gastrointestinal polyposis syndromes. In a polyposis

sis syndrome the combination of mucocutaneous lesions and oesophageal glycogenic acanthosis is considered diagnostic of Cowden's disease. Although GI lesions are benign and have no malignant potential it is crucial to identify these patients because the disease is inherited and carries a high risk of malignancy of the breast and thyroid.

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